

Sodium Channel Blockers Are Associated with Reduced Dementia Risk in Late-Onset Unexplained Epilepsy

C. Ferreira-Atuesta^{1,2}, K. M. Schubert^{1,2}, X. Y. Tai³, D. Noain^{1,4}, D. Skwarzynska^{1,4}, M. T. Wyss¹, S. Schreiner¹, H. H. Jung¹, T. Hedden⁵, J. Zelano⁶, T. Marson², G. Y. H. Lip², G. K. Mbizvo², M. Galovic¹

¹University Hospital & University of Zurich, CH • ²University of Liverpool, UK • ³University of Oxford, UK • ⁴ETH Zurich, CH • ⁵Mount Sinai, USA • ⁶University of Gothenburg, SE



BACKGROUND

Late-onset unexplained epilepsy (LOUE) may be both a harbinger and a driver of dementia.

LOUE carries **2–3× higher dementia risk¹**. Network hyperexcitability fuels amyloid-β release and tau spread^{2,3}; sodium-channel blockade lowers extracellular amyloid-β⁴. Non-levetiracetam ASM classes remain untested.

OBJECTIVE

Do specific ASM monotherapies differentially modify dementia risk in newly diagnosed LOUE?

METHODS

DESIGN

Target trial emulation

EXPOSURE

ASM monotherapy (new-user)

COMPARISON

4 classes / 5 agents vs. SV2A

DATA

TriNetX EHR network

OUTCOME

Incident dementia or Alzheimer's Disease

ADJUSTMENT

1:1 propensity matched

RESULTS

75.5M adults screened (≥55 yr) • **100k** with LOUE • matched arms **2-11k** per group • outcomes to **10 yr**

27% lower risk

of all-cause dementia
(HR 0.73, 0.61–0.88)

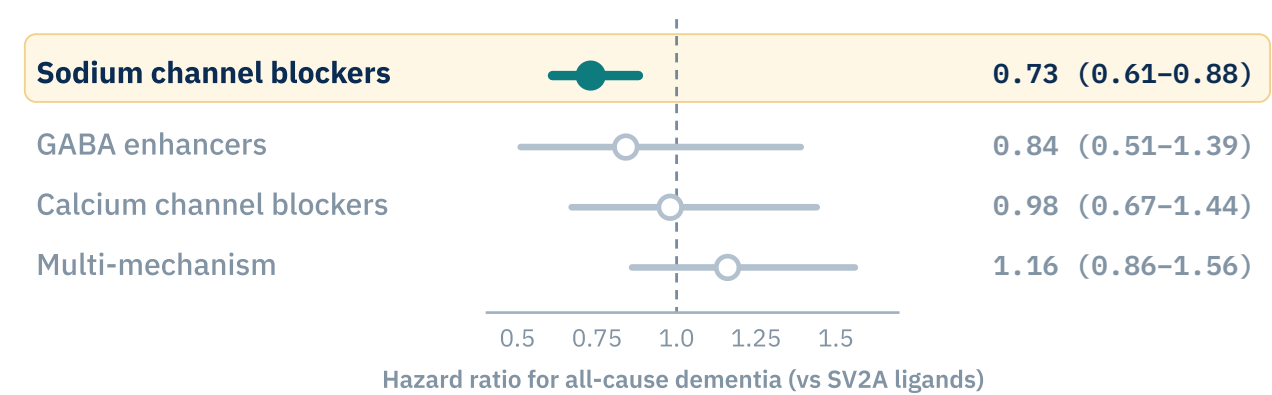
34% lower risk

of Alzheimer's disease
(HR 0.66, 0.49–0.88)

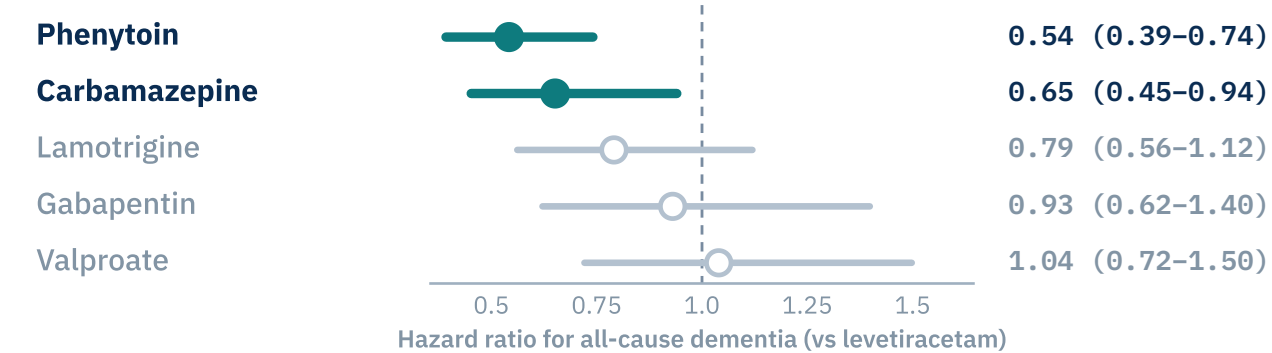
NNT 29

to prevent one
dementia case

All-cause dementia by mechanism class (vs SV2A ligands)



Individual ASMs, all-cause dementia (vs levetiracetam)



REPLICATION — sodium channel blockers vs. SV2A inhibitors

Down syndrome (n=10,548) **44% lower risk**
All-cause dementia

NACC external (n=279) **72% lower risk**
MCI or dementia

PAIRWISE AGENTS — dementia or death

	Phen.	Carb.	Lam.
Phenytoin	REF	1.10 (0.49–2.45)	1.21 (0.93–1.56)
Carbamazepine		REF	1.13 (0.85–1.48)
Lamotrigine			REF

HR (95% CI) for the **row** agent vs the **column** agent.

KEY FINDINGS

Sodium channel blockers are associated with reduced dementia risk in LOUE : 27% lower dementia and 34% lower Alzheimer's vs. SV2A ligands.

Phenytoin and **carbamazepine** show the strongest individual associations; **lamotrigine** offers the best efficacy–safety balance.